DOI: 10.1002/hon.3079

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LETTER TO THE EDITOR

Reply to "successful early use of anti-SARS-CoV-2 monoclonal neutralizing antibodies in SARS-CoV-2 infected hematological patients—A Czech multicenter experience": A case series of SARS-CoV-2 Omicron infection and aggressive lymphoma in the Sotrovimab era

Abstract

A prospective multicentre experience of early administration of anti-SARS-CoV-2 spike protein neutralizing monoclonal antibodies (MA) with efficacy among patients with hematological malignancies and early-stage COVID-19 was reported by Weinbergerová et al. The study validated the safety and efficacy of MA early use among hematological patients with newly diagnosed early-stage COVID-19 in terms of alleviating infection course and decreasing mortality. However no reference to new variant (Delta and Omicron) or other MA (e.g., Sotrovimab) has been reported. We reported our monocentric experience of 8 aggressive lymphoma patients with Omicron infection, 7 of whom treated with this MA in our Institution between December 2021 and February 2022. Among the patients treated with Sotrovimab nobody experienced neither SARS-CoV2 reactivation, nor other infectious events. One patients on active lymphoma treatment was hospitalized for pneumonia and treated with remdesivir. In 4/8 patients negativization of molecular swab occurred concomitantly to symptoms resolution with a median of 5.25 days, while the other 4 patients remained persistently positive with a median of 26.3 days. In this group, in order to maintain the chemo/chemo-immunotherapy (CT/CIT) dose-density, lymphoma treatment was reassumed independently on molecular swab analysis. SARS-CoV-2 negativization occurred with a median of 7.7 days after the resumption of CT/CIT. The one patient treated with remdesivir, although still positive to molecular swab, restarted R-COMP regimen at symptoms resolution too, but experienced an Omicron pneumonia exacerbation. This is the first case series reported in literature of patients affected by Omicron variant in which Sotrovimab seems to provide a resolution of COVID-19 disease, even in patient with molecular swab positive persistence too. Patients with aggressive lymphoma histologies should not be deprived of the best available treatment of their disease after sotrovimab administration, even in the presence of a still positive Omicron swab.

We read with interest the Letter by Weinbergerová et al.,[1] reporting their prospective multicentre experience of early administration of anti-SARS-CoV-2 spike protein neutralizing monoclonal antibodies (MA) with efficacy among patients with hematological malignancies (HM) and early-stage COVID- 19. Eighty-eight patients, including 30 lymphoma ones, were evaluated with a 97 days median follow-up after MA (bamlanivimab or casirivimab/imdevimab) administration. The authors observed rapid symptoms resolution (median duration of 2.5 days) after MA administration and a lower mortality rate in MA treated cohort respect "remdesivir/convalescent plasma naïve" patients. Notably, 63% of patients received rituximab or chemotherapy in the previous 2 years. The study validated the safety and efficacy of MA early use among hematological patients with newly diagnosed early-stage COVID-19 in terms of alleviating infection course and decreasing mortality.[1] However no reference to new emerging variant (e.g., Omicron) or other MA has been reported (Figure 1).

To date, since its first occurrence in December 2019, SARS-CoV-2 pandemic has spread aggressively worldwide being more destructive in some higher risk groups,[2] such as elderly with peak of mortality exceeding 8% in >80 years old and cancer patients being HM particularly associated with severe COVID-19 disease. A mortality rates of 13% and 23% at 30 and 100 days respectively[3] was documented in lymphoma patients, reaching up 35% in hospitalized ones.[4,5] Efforts in preventing severe COVID-19 disease have been carried out especially in such frail patients in term of vaccination program. Nonetheless, seroconversion rate was reduced compared to

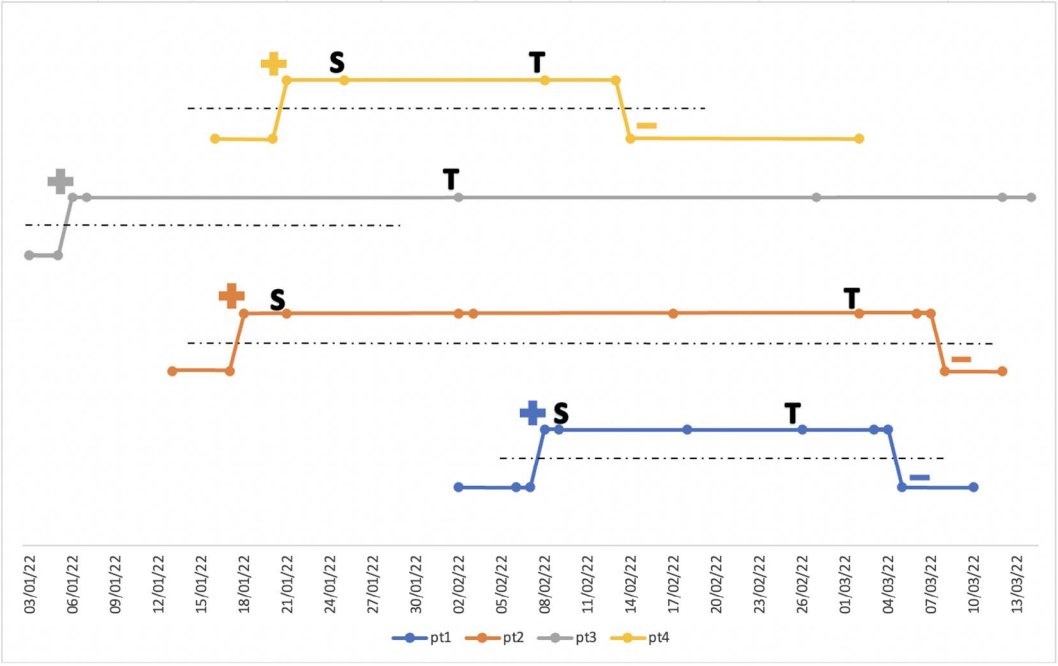

FIGURE 1 Clinical course and of the 4 patients that restarted lymphoma treatment despite molecular swab till positive. S: sotrovimab administration. T: lymphoma treatment reassumption. +: swab positivity. -: swab negativity. +: symptoms onset

general population (65%–69%),[6,7] particularly in receivers anti-cancer treatments <12 months (55%)[6] with the lowest value reported in those treated with anti-CD20 antibody-based chemo-immunotherapy (17.6%). Together with the latter, aggressive B-cell lymphoma diagnosis, emerged in multivariate analysis as independent negative predictors for seroconversion.[6] Several MA against SARS-CoV2 spike protein[8,9] were developed in order to mitigate COVID-19-related morbidity/mortality. A new SARS-CoV-2 immune-evading variant named Omicron (B.1.1.529)[10] emerged in November 2021. It presents more than 30 mutations on the spike protein so being able to confer resistance against most of the overmentioned MA,[11] but conferring a lower disease severity in cancer patients than previous virus variants.[12] Sotrovimab, that recognizes an epitope not substantially altered in Omicron variant, reduces of 85% the risk of progression in severe COVID19 disease, if administered early in mild symptomatically high risk outpatients.[13] Based on these considerations, an emerging unmet need is how to behave in patients actively treating for aggressive lymphoma and concomitant Omicron COVID-19 infection. With the aim to evaluate Sotrovimab efficacy, we collected data of 8 aggressive lymphoma patients affected by Omicron, 7 of whom treated with this MA in our Institution between December 2021 and February 2022. Clinical and laboratory characteristics are detailed in Table 1. Seven patients were male (M/F = 7/1) with median age of 55 years (range 25–84). Histologies were very variable in terms both of prognosis and treatment; five patients received anti CD-20 treatment in association with chemotherapy. All patients had received at least two doses of mRNA vaccine Pfizer, with 50% of them have completed vaccine cycle with third dose before lymphoma treatment start. Median value of anti-spike dosage was 386,5 (IQR 173–886) U/mL. Considering time of Omicron occurrence, it was observed in 7/8 (88%) of patient after lymphoma treatment start, with a median of 2.8 (IQR 1–5) cycles, while in the remaining one occurred in the time between lymphoma diagnosis and therapy introduction. All patients presented with mild-to-moderate COVID-19 infection and reported promptly (≤24 h) their symptoms to our hematology clinic. They were referred to the Infectious Disease department of our hospital where molecular nasal swab to detect SARS-CoV-2 variant type was performed. Omicron was identified in 100% of cases and 88% of them as outpatients, received treatment with a single infusion of Sotrovimab 500 mg IV after a median time of 4.7 (IQR 3–7) days after symptoms onset. The use of prognostic model recently validated on a large population of lymphoma patients in Italy[3] allowed to stratify our COVID-19 patients into 3 groups with extremely different survival expectations. Only 3 patients belonged to the low-risk group, while 5/8 presented an expected 30-days mortality of 22% and 45% falling into intermediate- and high-risk group respectively. The only patient requiring hospital admission because of documented pneumonia,[14] was treated with Remdesivir 200 mg IV loading dose on day one, followed by a 100 mg IV maintenance dose for additional 4 days. Median time of symptoms resolution was of 4.25 (IQR 1–12) days while SARS-CoV2 molecular swab negativization occurred in 24.7 (IQR 16–50) days. Notably, the one patient treated with only remdesivir presenting a positivity persistence at 3 months, still at the latest follow-up. Considering the 7 patients who had already started chemo +/−immunotherapy, lymphoma treatment was resumed at time of both resolution of symptoms and recovery of blood counts. The average delay for the expected recycling was of 11.5 days (range

TABLE 1 Clinical and laboratory description of the 8 patients with aggressive lymphoma and Omicron infection

	Age	Sex	Lymphoma histology	Lymphoma treatment	Lymphoma treatment status at Covid-19 diagnosis	Lymphoma diagnosis to Covid-19 (time in months)	Covid-19 related symptoms	Sotrovimab administration	Time from illness to viral clearance (days)	Duration from illness to clinical recovery (days)	Anti-spike antibodies title	VISCO et al scoring system for prognosis	Hospital admission	Disease status at the latest follow-up
1	56	M	Primary CNS lymphoma	MATRIX	3° cycle	≤3 months	Fever, cough	Yes	27	3	886 U/mL	3 (male gender, ALC ≤650, PLT <100)	No	CR
2	83	M	DLBCL, Waldenstrom macroglobulinemia	Bendamustina-Rituximab; R-COMP	5° cycle	3–12 months	Fever	Yes	50	4	260 U/mL	5 (age ≥65, male gender, ALC ≤650, PLT <100)	No	PD
3	84	M	DLBCL	R-COMP	1° cycle	≤3 months	Fever, asthenia	No	Not applicable	4	227 U/mL	3 (age ≥65, male gender)	Yes	PR
4	43	F	PMBCL	R-DA-EPOCH	1° cycle	≤3 months	Fever, cough, rhinorrhea	Yes	25	4	Not applicable	1 (ALC ≤650)	No	CR
5	32	M	HL	ABVD	5° cycle	3–12 months	Fever	Yes	18	1	173 U/mL	1 (male gender)	No	CR
6	25	M	DLBCL	R-CHOP	3° cycle	≤3 months	Cough, pharyngodynia	Yes	19	12	Not applicable	1 (male gender)	No	CR
7	31	M	HL	ABVD	2° cycle	≤3 months	Rhinorrhea	Yes	16	2	Not applicable	2 (male gender, ALC ≤650)	No	CR
8	83	M	PTCL-NOS	COMP	Before therapy	≤3 months	Fever	Yes	18	4	Not applicable	3 (age ≥65, male gender)	No	PD

Abbreviations: ABVD, adriamycin; bleomycin, vinblastine and dacarbazine.; COMP, cyclophosphamide; CR, complete response; cyclophosphamide, and vincristine.; DA-EPOCH, dose adjusted-etoposide; DLBCL, diffuse large B cell lymphoma.; HL, Hodgkin lymphoma.; liposomial, doxorubicin; PCNSL, primary central nervous system lymphoma.; PD, progressive disease.; PMBCL, primary mediastinal B cell lymphoma.; PR, partial response.; prednisone, doxorubicin; PTCL-NOS, primary T cell lymphoma not otherwise specified.; R, rituximab.; vincristine, and prednisone.

0–20 days). Among the patients treated with Sotrovimab nobody experienced neither SARS-CoV2 reactivation, nor other infectious events. In 4/8 patients negativization of molecular swab occurred concomitantly to symptoms resolution with a median of 5.25 (IQR 3–7) days, while the other 4 patients remained persistently positive with a median of 26.3 (IQR 9–46) days. In this group, in order to maintain the chemo/chemoimmunotherapy (CT/CIT) dose-density, lymphoma treatment was reassumed independently on molecular swab analysis (Figure 1). SARS-CoV-2 negativization occurred with a median of 7.7 (IQR 6–10) days after the resumption of CT/CIT. The one patient treated with remdesivir, although still positive to molecular swab, restarted R-COMP regimen at symptoms resolution too. No infection occurred after the second CIT cycle. Unexpectedly, after the third cycle a symptomatic SARS-CoV2 pneumoniae was documented at broncho-alveolar lavage without evidence of other infections, suggesting COVID-19 reactivation then successfully treated. At a median follow-up of 76 (IQR 46–101) days no early death was registered. Considering response to hematological treatment at interim/end-of-treatment evaluation, we reported 5 complete response and 2 progressive disease, notably observed in a group of patients with a expected poor prognosis. The only patient in partial response is the elderly one with diffuse large B cell lymphoma that experienced COVID-19 reactivation.

Here we described for the first time, the clinical management of an aggressive lymphoma series with concomitant Omicron SARS-CoV-2. The main aim in this curative setting of patients was to maintain efficacy of hematological treatment despite viral infection. Nowadays, there is no clear definition of when patients with HM can be considered healed from COVID-19. In fact, longer duration of disease and thereby prolonged detection of SARS-CoV2 in respiratory specimens (up to 85 days in lymphoma patients)[15] raise some concerns, especially in patients necessarily to treat. A long-term viral persistence in upper airways may allow the virus to develop several mutations on surface proteins to elude immune surveillance but a positive polymerase chain reaction test could also persist for a long period without active infection.[16] Therefore, the decision to re-challenge anti-lymphoma treatment in absence of symptoms of active viral COVID-19 infection should be individualized since off sure, viral persistence, reactivation, or re-infection with novel variants of SARS-CoV-2 could be a potential risk.[17] Also regarding timing of resuming antineoplastic therapies, there are no data. In the few available case-reports, hematological treatment was administer only after negativization of molecular swab.[18] In the largest experience of MA reported, among 13 patients described with HM, two cases of COVID-19 affected by aggressive lymphomas have received both remdesivir and casirivimab/imdevimab with resolution of infection and molecular negativization. Information regarding active treatment were not mentioned. In all the forementioned reports, MA have been used with a more prolonged time lapse from symptoms onset. The importance of prompt intervention with MA was highlighted, as in our series, also in the Czech multicenter experience, where with a median of 1.4 days from COVID-19 diagnosis to MA administration, a lower rate of severity progression or death was reported.[1] The only patient treated in our series with antiviral agent, experienced recurrence of COVID-infection on active cancer treatment. Conversely, considering patients affected by Omicron variant, Sotrovimab seems to provide a resolution of COVID-19 disease, even in patient with molecular swab positive persistence too. In this way, it might cautiously be suggested that patients with aggressive lymphoma histologies should not be deprived of the best available treatment of their disease after sotrovimab administration, even in the presence of a still positive Omicron swab. This point, if confirmed in the future by prospective and solid data, could paved the way on MA use not only to reduce COVID morbidity/mortality risk, but also to aim to preserve the intensity of lymphoma treatment.

AUTHOR CONTRIBUTIONS

Ramona Cassin and Nicolò Rampi designed the study, collected and analyzed data, composed and revised manuscript; Cecilia Fidanza, Alessandro Noto and Francesca Gaia Rossi contributed to study design and collected data; Andrea Muscatello and Bianca Mariani collected data and contributed to composed manuscript; Luca Baldini composed and critically reviewed and approved the final manuscript. All authors read and approved the final version of the manuscript.

KEYWORDS

aggressive lymphoma, monoclonal antibody, omicron, SARS-CoV-2

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/hon.3079.

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